REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims.

Applicants have amended claims 1, 3, 4, 8, 13, 18, 22, 24, 28, 35, 38-40, 50, 58, 61-64, 68, 74, 84-85, 88, 90, 101, 106-107, 111, 116, 122, 125 and 127. Applicants have amended claim 1 to clarify the subject matter of the claim, insert full descriptions of acronyms and to correct grammatical errors. Applicants have amended claims 3, 22, 24, 68, 84, 106, 122, 125, and 127 to correct typographical errors. Claims 4, 13, 18, 28, 40, 58, 85, 88, 107, and 116 are amended to provide antecedent basis and to remove nonelected subject matter. Claims 61, 63-64, and 122 are amended to change claim dependency and provide antecedent basis. Claims 8, 35, 38-39, 50, 62, 74, 90, 101, and 111 are amended to clarify the subject matter of those claims. No new matter has been added by the amendments.

Applicants have cancelled claims 75-81 and 128 without prejudice. Claims 75-81 are cancelled due to a restriction requirement. Applicants reserve the right to pursue the subject matter of claims 75-81 and 128 in a divisional or in a continuation application.

Applicants have amended the specification to correct typographical errors, add trademark designations, and remove a hyperlink.

Interview Summary

Applicants thank Examiner Huynh for the interview conducted on September 19, 2006. We discussed the 112 and 102 rejections.

Objection to the Specification

The Examiner objects to the specification due to the presence of a hyperlink of an internet website. Applicants have removed the hyperlink from the specification. Applicants respectfully request removal of this objection.

Objection to the Claims

The Examiner objects to claims 4, 13, 28, 40, 58, 85, 88, 107, and 116 for reciting a non-elected embodiment. Applicants have amended claims 4, 13, 28, 40, 58, 85, 88, 107, and 116 to

no longer refer to a non-elected embodiment. Applicants respectfully request removal of this objection.

Rejections under 35 U.S.C. § 112, first paragraph (Enablement)

The Examiner rejects claims 1-74 and 82-127 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Examiner has several bases for the rejection. The Examiner contends that:

a) the specification does not provide enablement for expressing a variable domain of an antibody or antigen binding fragment thereof comprising one or more modified framework regions;

b) the specification does not provide enablement for a method for preparing any humanized antibody or antigen binding fragment thereof;

c) the specification does not provide enablement for a method for improving the yield of any antibody or antigen binding fragment comprising one or more modified FR, wherein the at least one modified FR has at least 50% sequence identity to any corresponding FR of the selected subgroup consensus sequence; and

d) claims 1, 18, 19, 25, 29, 38, 49, 82, 92, 96, 104, 117 and 127 lack enablement for failure to provide structure of amino acid sequences with sequence identifiers and to identify which amino acid positions of the FRs would result in increased yields. Applicants respectfully traverse.

To meet the enablement requirement of 35 U.S.C. §112, first paragraph, a specification must contain a sufficient description to enable one skilled in the art to make and use the claimed invention (*See, e.g., Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004); MPEP §2164.01). A specification does not need to explicitly disclose every detail, and may omit what is well known in the art (*In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP 2164.01). To make and use an invention may require experimentation even if the specification is enabling (*In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984); MPEP §2164.01). The experimentation must not be unduly extensive (*Id.*), however, costly and timely experimentation alone does not constitute undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir.

1988)). In establishing a *prima facie* case of nonenablement, the Examiner has the burden of setting forth a reasonable explanation of why the claimed scope is not enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-1562 (Fed. Cir. 1993).

a) Claims 1-24 and 50-70

The Examiner rejects claims 1-24 and 50-70 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Examiner asserts that the specification is not commensurate in scope with claims as how to produce any antibody or antigen binding fragment in high yield by expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified FR in a host cell. Applicants respectfully traverse.

Applicants' claim 1 is directed to a method for producing an antibody or antigen binding fragment in high yield from the host cell, comprising: a)expressing a variable domain of the antibody or antigen binding fragment comprising at least one modified framework region (FR) in the host cell, wherein the at least one modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the at least one amino acid position and the different amino acid are determined by selecting a human subgroup variable domain consensus sequence that has a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of a corresponding position of the FR of the antibody or antigen binding fragment, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region; and b)recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell. Claims 2-24 depend from claim 1.

Claim 50 is directed to a method for producing an antibody or antigen binding fragment in high yield from a host cell comprising :a)expressing a modified variable domain of the antibody or antigen binding fragment in the host cell, wherein the modified variable domain has a substitution of at least one amino acid position proximal to a cys residue that participates in an

intrachain variable domain disulfide bond with a different amino acid, wherein the different amino acid is determined by selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position proximal to the cys residue in the selected human subgroup variable domain consensus FR sequence having a different amino acid than that found at a corresponding position of the antibody or antigen binding fragment's variable domain, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified variable domain; and b)recovering the antibody or antigen binding fragment comprising the modified variable domain from the host cell. Claims 51 to 70 depend from claim 50.

The Examiner contends that the amino acid sequences must be identified with an appropriate sequence identifier and further that locations of and the type of amino acids must be specified. Applicants respectfully disagree.

With regard to the amino acid sequences of the framework regions and the variable domains of antibodies or antigen binding fragments thereof, Applicants submit that these sequences are known to those of skill in the art or can readily be determined using standard methods. As described in the specification, variable domain sequences of many antibodies are known or can be readily determined. For example, the Kabat database and other databases provide for the sequences of thousands of antibodies. The Kabat publications also provide the sequences of many antibodies. The human subgroup consensus sequences can be derived from the sequences of antibodies in the subgrouping as provided in the Kabat publications and in other databases. See page 35, lines 1-11. Moreover, Applicants submit that they have provided examples of sequences of the variable domains of antibodies as well as the subgroup consensus sequence for the FR1, HVR1, HVR2, HVR3 of the human heavy chain variable domain consensus sequences. See e.g. Figures 15-23.

In the case of *Falko-Gunter Falkner vs. Inglis*, 448 F.3rd 1357, the Federal Circuit indicated that the claims are enabled if the specification indicates that sequences are known to

those of skill in the art so that one of skill in the art can readily identify sequences. Therefore, the specification need not teach that which is known in the art in order to enable the claims.

Moreover, Applicants submit that they have disclosed the location of the amino acid positions and the type of substitution. Applicants teach selecting a human subgroup variable domain consensus sequence by comparing the sequence of HVR1 and/or HVR2 of the human subgroup variable domain consensus sequences with the antibody or antigen binding fragment's HVR1 and/or HVR2. The human subgroup variable domain consensus sequence that shares the most sequence identity to the HVR1 and/or HVR2 of the antibody or antigen binding fragment thereof is selected. See Specification, e.g. Examples 2-5 at pages 68-88. The selected human subgroup variable domain consensus sequence FR sequence is aligned with the FR of the antibody or antigen binding fragment thereof, and amino acid positions that differ are identified as the amino acid positions that can be substituted. The amino acids substituted at those positions are those that are found at the corresponding FR position in selected human subgroup variable domain consensus sequence. See e.g. the specification at page 34, line 23, to page 35, line 20. In addition, Applicants have described and identified where specific substitutions should be made. See e.g. page 35, lines 21-31. Applicants have provided working examples with at least 4 different antibodies each having different sequences and substitutions. See e.g., examples 1-5

Applicants have also taught how to express said humanized antibody or antigen binding fragment and determine whether the yield increases from said substitutions (see specification at Examples 2 to 6, including at p. 84, lines 5-33). The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." (*Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334, *citing*, *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) and *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991)). "[T]he mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art." *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006).

Based on the foregoing, Applicants request withdrawal of the rejection.

b) Claims 25-37 and 71-73

The Examiner rejects claims 25-37 and 71-73 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Examiner asserts

> [e]nablement is not commensurate in scope with claims as how to produce any antibody or antigen binding fragment in high yield by expressing a variable domain of the antibody or antigen binding fragment comprising expressing at least one modified framework regions (FR) from *light chain* wherein the modified FR has a substitution of at least one amino acid position with a different amino acid found at the corresponding FR of a human subgroup variable domain consensus sequence that has a **HVR1** (heavy chain variable region 1) and/or **HVR2** (heavy chain variable region 2 (claims 1, and 7). Office Action, May 3, 2006 at p. 6. [emphasis in original].

As an initial matter, Applicants direct the Examiner's attention to the specification at page 21, lines 12-25. HVR does not describe a heavy chain variable region but rather a hypervariable region that can found in both heavy and light chain variable domains. Thus, both the heavy chain and the light chain variable domains each comprise three HVRs: HVR1(that may include amino acids of CDR1 as defined by Kabat); HVR2(that may include amino acids of CDR2 as defined by Kabat); and HVR3(that may include amino acids of CDR3 as defined by Kabat) .

Secondly, the Examiner asserts that the specification does not disclose replacing at least one amino acid in at least one framework region of the light chain. Applicants submit that they have described substituting at least one amino acid in a light chain. See e.g. page 35, lines 21-27. See also pages 16-17. In addition, Applicants have provided at least one working example with substitutions in the light chain. See e.g. Example 6 at page 90, lines 8-14, and page 91, lines 6-8.

The Examiner further contends that the number and type of amino acid substitutions is unlimited and that there is no guidance as to which substitutions will enhance yield. Applicants respectfully disagree.

The claims are directed to producing an antibody or antigen binding fragment thereof in high yield comprising expressing a variable domain of the antibody comprising at least one modified FR region. At least one FR region can be modified at one or more amino acid positions that are identified by aligning the antibody or antigen binding fragment thereof's FR region with

the corresponding FR of the selected human subgroup variable domain consensus sequence. Each FR has approximately 10 to 30 amino acids. Within each FR region, the maximum number of amino acids substituted will be the number of amino acids in the FR region. For definition of FR regions, see page 21, line 26 in the specification. For the amino acids substituted at the positions, the amino acid substituted at any particular position is the amino acid that corresponds to the amino acid at the corresponding position in the selected subgroup human variable domain consensus sequence. Thus, applicants submit that the number and type of substitutions is not unlimited.

Moreover, Applicants have provided a working example showing that the substitution of FR1, FR1 and FR2, and FR1 and FR2 and FR3 in an antibody all lead to an increase in yield. See e.g. the specification at page 96. These antibodies have multiple substitutions in each of these framework regions and the yield was increased in each case.

Based on the foregoing, Applicants request withdrawal of the rejection on this basis.

c) Claims 50-74 and 100-103

The Examiner rejected claims 50-74 and 100-103. The Examiner contends that the amino acid sequence with appropriate sequence identifiers are required. The Examiner further contends that there is insufficient guidance as to which amino acids are to be substituted for the positions proximal to a cys. Applicants respectfully disagree.

With regard to the identification of sequences of variable domains, Applicants submit that many sequences of variable domains are known to those of skill in the art or can be readily determined. The specification also discloses 9 different nucleic acid and polypeptide sequences in Figures 15-23. Applicants have provided a working example describing how to identify residues proximal to cys residues and make substitution at those positions. See e.g. Example 6.

In the case of *Falko-Gunter Falkner vs. Inglis*, 448 F.3rd 1357, the Federal Circuit indicated that the claims are enabled if the specification indicates that sequences are known to those of skill in the art so that one of skill in the art can readily identify sequences. Therefore the specification need not teach that which is known in the art in order to enable the claims.

Secondly, Applicants submit that they have taught a number of methods for identifying amino acid positions proximal to a cys residue including using a crystal structure of an antibody or by molecular modeling using techniques and programs known to those of skill in the art. See

the specification, e.g., at page 23 , lines 7-27. Moreover, Applicants submit the crystal structures of many antibodies are known and available in the Protein Databank (PDB)database and other databases.

Finally, the Examiner contends there is no guidance as to which amino acids will be substituted at the position. Applicants disagree. Claim 50 provides that the different amino acid that is at the substituted at at least one amino acid position proximal to a cys residue position as an amino acid found at the corresponding position in the selected human variable domain subgroup consensus sequence. Thus, the amino acids that are substituted at the position proximal to a cys residue are readily identifiable by reference to the selected human variable domain subgroup consensus sequence.

Based on the foregoing, Applicants request withdrawal of the rejection on this basis.

d) Claims 1, 18-19, 25, 29, 38, 49, 82, 92, 96, 104, 117 and 127

Claims 1, 18-19, 25, 29, 38, 49, 82, 92, 96, 104, 117 and 127 were rejected by the Examiner for lack of enablement. The Examiner contends that there is a lack of guidance as to the location and guidance of the amino acids to be substituted as well as the mixture of framework regions. Applicants respectfully disagree.

With respect to the location guidance as to type of amino acids that will be substituted as well as the sequences of variable domain, Applicants have addressed this rejection previously. Please incorporate the arguments raised above.

With respect to the mixture of differing FR regions, Applicants submit that one of skill in the art would know how to make and use the claimed antibodies. Applicants have described the location of the FR regions. See the specification at e.g. at page 21, lines 26 to page 22, line 6. Applicants have described how to identify an amino acid position in each FR for substitution. See e.g. page 35, lines 11-19. Applicants have described how to derive a human consensus sequence for each human variable domain subgroup and have provided at least the sequence of the heavy chain FR1 of each of the human heavy chain subgroups. Applicants note that the number of subgroups of human antibodies is known: for human heavy chain variable domains there are three subgroups and for human kappa light chain variable domains there are four subgroups. Applicants have described how to select amino acids to be substituted at each amino acid position in each FR region. Applicants have provided a working example showing that

modification of FR1, FR1 and FR2, and FR1 and FR2 and FR3 provides an increase in yield of the antibody. See e.g. page 96 of the specification. Thus, Applicants submit the specification enables the claimed subject matter.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement.

Rejections under 35 U.S.C. § 112, first paragraph (Written Description)

The Examiner rejects claims 1-74 and 82-127 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description. The Examiner asserts that the claims contain subject matter that was not described in the specification to reasonably convey possession by the Applicants. Specifically, the Examiner asserts that the specification does not adequately specify (1) the structure of the heavy and light chain variable domain of any and all antibodies claimed by the method, (2) which heavy chain or light chain framework residues can be modified, (3) the type of amino acids to be substituted at the recited positions, and (4) the position or the location of the amino acids with the FR or mixture of FR to be substituted. Applicants respectfully traverse.

As noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) *Fed Reg.* 1099, 1105 (2001); *see also, In re Wertheim,* 191 USPQ 90,97 (CCPA 1976). The guidelines further state that "[(The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." 66(4) *Fed. Reg.* at 1107; 191 USPQ at 97, (emphasis added). Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow,* 217 USPQ 1089 (Fed. Cir. 1991).

From her rejection, the Examiner seems to take the position that written description requires precise sequence information and actual reduction to practice of every embodiment. However, the Federal Circuit has maintained that precise sequence information and actual reduction to practice of every embodiment is not necessary to meet the written description requirement.

> "The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed" 418 F.3d 1349, 1357 (Fed. Cir. 2005) The Board was correct, however, not to view as dispositive that Inglis had not actually produced a poxvirus vaccine, [n10] because an actual reduction to practice is required for written description.
> *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006).

Moreover, the Federal Circuit in the same case also stated that recitation of known structure is not required to satisfy written description. The court indicated where accessible literature sources provide sequences, satisfaction of written description does not require recitation of sequences in the specification. *Falkner v. Inglis*, 448 F.3d 1357, 1363

Applicants further submit that they have provided the sequences of 9 different antibodies and that many other sequences are known to those of skill in the art. Applicants have provided working examples of at least one substitution in a FR region for at least 4 different antibodies. Applicants have described that the location of the amino acids to be substituted are those that when aligned with the corresponding selected human subgroup consensus FR sequence differ from that of the antibody or antigen binding fragment. The amino acid substituted at that position is the amino acid in the corresponding position of the selected subgroup consensus sequence. Thus, Applicants submit that one of skill in the art reading the specification would understand that Applicants were in possession of the claimed subject matter.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1, 8, 12, 28, 35, 39, 40, 63, 64, 74, 88, 101, and 111 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse.

a) The Examiner rejects claim 1 for using the abbreviations "HVR1", "HVR2", and "FR" without establishing the full terminology. Applicants have amended claim 1 to refer to the full terminology. Applicants respectfully request removal of this rejection.

b) The Examiner rejects claims 8, 101, and 111 contending the claims recite a polynucleotide comprising an expression vector. While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended dependent claims 8, 101, and 111 to recite that the polynucleotide is comprised within an expression vector. Applicants respectfully request removal of this rejection.

c) The Examiner rejects claim 12 for alleged indefiniteness regarding the recitation of "HVR1 amino acid sequence". Applicants believe the Examiner made a typographical error, and that this rejection actually is directed to claim 13. While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 13 to refer to the HVR1 sequence of the variable domain of the antibody or antigen binding fragment thereof. Applicants respectfully request removal of this rejection.

d) The Examiner rejects claim 28 for alleged indefiniteness regarding the recitation of "HVR1 amino acid sequence". While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 28 refer to the HVR1 sequence of the variable domain of the antibody or antigen binding fragment thereof. Applicants respectfully request removal of this rejection.

e) The Examiner rejects claim 35 due to an alleged lack of antecedent basis for the term "both". While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 35 to replace "both" with "the full-length heavy chain and the full-length light chain". Applicants respectfully request removal of this rejection.

f) The Examiner rejects claim 39 due to an alleged lack of antecedent basis for the term "said at least one FR". As suggested by the Examiner, Applicants have deleted the term "said". Although not specified by the Examiner, Applicants have replaced "the" in line 4 with "a". Applicants respectfully request removal of this rejection.

g) The Examiner rejects claim 40 for alleged indefiniteness regarding the recitation of "HVR1 amino acid sequence". While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 40 refer to the HVR1 of the variable domain of the antibody or antigen binding fragment thereof. Applicants respectfully request removal of this rejection.

h) The Examiner rejects claim 61 since the term "first and second polynucleotide" allegedly does not have antecedent basis in base claim 50. Applicants have amended claim 61 to depend upon claim 60. Antecedent basis for a "first polynucleotide" can be found in claim 50 (from which claim 60 depends upon), and antecedent basis for a "second polynucleotide" can be found in claim 60. Applicants respectfully request removal of this rejection.

i) The Examiner rejects claim 63 since the term "heavy chain variable domain" does not have antecedent basis in claims 51 or 60. Applicants have amended claim 63 to depend upon claim 62, which provides antecedent basis for the term "heavy chain variable domain". Applicants respectfully request removal of this rejection.

j) The Examiner rejects claim 64 since the term "light chain variable domain" does not have antecedent basis in claims 51 or 60. Applicants have amended claim 63 to depend upon claim 62, which provides antecedent basis for the term "light chain variable domain". Applicants respectfully request removal of this rejection.

k) The Examiner rejects claim 74 for allegedly being incomplete for failing to achieve the goal set forth in the preamble. While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended the claim to also recite "expressing said antibody or antibody fragment thereof." Applicants respectfully request removal of this rejection.

l) The Examiner rejects claim 88 for alleged indefiniteness regarding the recitation of "HVR1 amino acid sequence". While not acquiescing to the rejection and solely to expedite prosecution, Applicants have amended claim 88 refer to the HVR1 of the variable domain of the antibody or antigen binding fragment thereof. Applicants respectfully request removal of this rejection.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

Rejections under 35 U.S.C. § 102(b/e)

The Examiner rejects claims 1-20, 22-42, 44-49, 71-73, 82-99, 104-123, and 125-127 under 35 U.S.C. § 102(b) or § 102(e) as allegedly anticipated by at least one of 1)WO 98/45331, 2)U.S. Patent No. 6,884,879 ('879), 3)Forsberg et al., *J. Biol. Chem.* (1997), 4)Presta et al., *Cancer Res.* (1997), 5)Baca et al., *J. Biol. Chem.* (1997), and 6)Chen et al., *J. Mol. Biol.* (1999). Applicants respectfully traverse.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." *Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *See also*, MPEP §2131.

1) ***WO 98/45331.***

The Examiner rejects claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127 under 35 U.S.C. § 102(e) for alleged anticipation by WO 98/45331. Applicants respectfully traverse.

Claim 1 is directed to a method of producing an antibody or antigen binding fragment thereof with high yield from the host cell by (a) expressing a variable domain that has at least one modified FR in the host cell, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the at least one amino acid position and the different amino acid are determined by selecting a human subgroup variable domain consensus sequence that has a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of a corresponding position of the FR of the antibody or antigen binding fragment, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region ; and b)recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell. Each of claims 2-18, and 22-24 depends directly or indirectly on claim 1, and thus shares the above-described claim elements to claim 1. Claims 25-41, 44-49, 82-99, 104-121, and 125-127 generally recite either that the FR

region(s) itself or modification(s) within the FR region(s) in the antibody or antigen-binding fragment are taken from the FR region(s) of a selected human subgroup consensus sequence that has an HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the antibody or antibody binding fragment.

WO 98/45331 does not teach all of the elements of claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127. At the least, WO98/45331 does not teach comparing the HVR1 and/or HVR2 of the antibody or antibody binding fragments to human HVR1 and/or HVR2 sequences of different human subgroup consensus sequences. Furthermore, WO98/45331 does not teach selecting FR amino acid positions for substitution that are identified by comparing the antibody or antigen binding fragment FR sequences with the FR sequences of the corresponding selected human consensus subgroup. In addition, WO 98/145331 does not teach that the amino acid that is substituted at the identified position is the amino acid found at the corresponding position of the selected human subgroup consensus sequence. In contrast, WO98/45331 substituted FR residues with the murine residues of the murine antibody from which the CDR sequences were derived (see, e.g., Example 1) or by randomizing FR residues using phage display (see, e.g., Example 2).

Therefore, WO 98/45331 does not disclose each and every element of the claims, and as such, does not anticipate claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127. Applicants respectfully request reconsideration and withdrawal of this rejection.

2) ***U.S. Pat. No. 6,884,879.***

The Examiner rejects claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127 under 35 U.S.C. § 102(e) for alleged anticipation by U.S. Patent No. 6,884,879. Applicants respectfully traverse.

Claim 1 is directed to a method of producing an antibody or antigen binding fragment thereof with high yield from a host cell by (a) expressing a variable domain that has at least one modified FR in the host cell, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the at least one amino acid position and the different amino acid are determined by selecting a human subgroup variable domain consensus sequence that has a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of

the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of a corresponding position of the FR of the antibody or antigen binding fragment, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region ; and b)recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell. Each of claims 2-18, and 22-24 depends directly or indirectly on claim 1, and thus shares the above-described claim elements to claim 1. Claims 25-41, 44-49, 82-99, 104-121, and 125-127 generally recite either that the FR region(s) itself or modification(s) within the FR region(s) in the antibody or antigen-binding fragment are taken from the FR region(s) of a selected human subgroup consensus sequence that has an HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the antibody or antibody binding fragment.

The '879 patent does not teach all of the elements of claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127. At the least, the '879 patent does not teach comparing the HVR1 and/or HVR2 of the antibody or antibody binding fragments to human HVR1 and/or HVR2 sequences of different human subgroup consensus sequences. Furthermore, the '879 patent does not teach selecting FR amino acid positions for substitution that are identified by comparing the antibody or antigen binding fragment FR sequences with the FR sequences of the corresponding selected human consensus subgroup. In addition, the '879 patent does not teach that the amino acid that is substituted at the identified position is that amino acid found at the corresponding position of the selected human subgroup consensus sequence. In contrast, the '879 patent substituted FR residues with the murine residues of the murine antibody from which the CDR sequences were derived (see, e.g., Example 1) or by randomizing FR residues using phage display (see, e.g., Example).

Therefore, the '879 patent does not disclose each and every element of the claims, and as such, does not anticipate claims 1-18, 22-41, 44-49, 82-99, 104-121, and 125-127. Applicants respectfully request reconsideration and withdrawal of this rejection.

3) ***Baca et al.***

The Examiner rejects claims 25-27, 28-29, 31, and 33-36 under 35 U.S.C. § 102(b) as allegedly anticipated by Baca et al., *J. Biol. Chem.* (1997). Applicants respectfully traverse.

Claims 25-29, 31, and 33-36 generally recite either that the FR region(s) itself or modification(s) within the FR region(s) in the antibody or antigen-binding fragment are taken from the FR region(s) of a selected human subgroup consensus sequence that has an HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the antibody or antibody binding fragment.

Baca et al does not teach all of the elements of claims 25-29, 31, and 33-36. At the least, Baca et al. does not teach comparing the HVR1 and/or HVR2 of the antibody or antibody binding fragments to human HVR1 and/or HVR2 sequences of different human subgroup consensus sequences. Furthermore, Baca et al. does not teach selecting FR amino acid positions for substitution that are identified by comparing the antibody or antigen binding fragment FR sequences with the FR sequences of the corresponding selected human consensus subgroup. In addition, Baca et al does not teach that the amino acid that is substituted at the identified position is that amino acid found at the corresponding position of the selected human subgroup consensus sequence. In contrast, Baca et al teaches substituting FR residues with the murine residues of the murine antibody from which the CDR sequences were derived or by randomizing FR residues using phage display.

Therefore, Baca et al. do not disclose each and every claimed element, and as such, do not anticipate the claimed subject matter. Applicants respectfully request removal of this rejection.

4) ***Forsberg et al.***

The Examiner rejects claims 1-3, 6, 10, 12, 14, and 16-18 under 35 U.S.C. § 102(b) in view of Forsberg et al. Applicants respectfully traverse.

Claim 1 is directed to a method of producing an antibody or antigen binding fragment thereof with high yield from a host cell by (a) expressing a variable domain that has at least one modified FR in the host cell, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the at least one amino acid position and the different amino acid are determined by selecting a human subgroup variable domain consensus

sequence that has a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of a corresponding position of the FR of the antibody or antigen binding fragment, and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region; and b)recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell. Each of claims 2-3,6, 10, 12, 14 and 16-18 depend directly or indirectly on claim 1, and thus shares the above-described claim elements to claim 1.

Applicants respectfully submit that Forsberg et al. do not disclose all of the claimed elements. This reference does not teach a method for producing an antibody in high yield comprising expressing a variable domain of the antibody having a modified FR region, wherein the FR region is modified at at least one amino acid position by substituting the amino acid at that position with an amino acid from the selected human subgroup consensus sequence at that position. There was no discussion in this reference of utilizing human variable domain consensus sequences. Forsberg et al. teach the production of a chimera with a light chain from one Fab and a heavy chain from a different Fab, whereby the Fab differs from each other in the amount of Fab secreted. By a comparison of sequences of the light and heavy chains of each of the Fabs amino acid positions that affected yield were identified. Certain of these positions were not substituted because of the concern that they might affect antigen binding. The amino acids substituted at some of these positions were those of the heavy or light chain variable domain from the Fab that was secreted at a higher amount.

For at least this reason, the Forsberg et al. reference does not anticipate claims 1-3, 6, 10, 12, 14, and 16-18. Applicants respectfully request removal of this rejection.

5) ***Presta et al.***

The Examiner rejects claims 1-12, 14, 16-20, 25-27, 29, 31-33, 36-38, 41-42, 44, 46-49, 71-73, 82-85, 87, 89-92, 94-99, 104-109, 111, 115, 117, 119-123, and 125-126 under 35 U.S.C.

§ 102(b) as allegedly anticipated by Presta et al., *Cancer Res.* (1997). Applicants respectfully traverse.

Claim 1 is directed to a method of producing an antibody or antigen binding fragment thereof with high yield from a host cell by (a) expressing a variable domain that has at least one modified FR in the host cell, wherein the modified FR has a substitution of at least one amino acid position with a different amino acid, wherein the at least one amino acid position and the different amino acid are determined by selecting a human subgroup variable domain consensus sequence that has a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence with the most sequence identity with a HVR1 and/or HVR2 sequence of the antibody or antigen binding fragment's variable domain, and identifying at least one amino acid position in at least one FR of the selected human subgroup variable domain consensus sequence that has a different amino acid than that of a corresponding position of the FR of the antibody or antigen binding fragment ,and substituting the amino acid at the corresponding position of the antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form at least one modified FR region; and b)recovering the antibody or antigen binding fragment variable domain comprising the at least one modified FR from the host cell. Each of claims 2-12, 14, and 16-20 depend directly or indirectly on claim 1, and thus shares the above-described claim elements to claim 1. Claims 25-27, 29, 31-33, 36-38, 41-42, 44, 46-49, 71-73, 82-85, 87, 89-92, 94-99, 104-109, 111, 115, 117, 119-123, and 125-126 generally recite either that the FR region(s) itself or modification(s) within the FR region(s) in the antibody or antigen-binding fragment are taken from the FR region(s) of a selected human subgroup consensus sequence that has an HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the antibody or antibody binding fragment.

In the least, Presta et al. does not teach selecting positions for substitution that differ from the selected human subgroup consensus sequence or substituting the amino acid found at the corresponding position in selected human consensus subgroup. Presta et al. only describes substituting certain framework resides with an amino acid from the murine antibody from which the CDRs of the humanized antibody are derived. Therefore, Presta et al. do not disclose each

and every claimed element, and as such, do not anticipate the claimed subject matter. Applicants respectfully request removal of this rejection.

6) ***Chen et al.***

The Examiner rejects claims 25-26, 28, and 33-36 under 35 U.S.C. § 102(b) as allegedly anticipated by Chen et al., *J. Mol. Biol.* (1999). Applicants respectfully traverse.

Claims 25-26, 28, and 33-36 generally recite either that the FR region(s) itself or modification(s) within the FR region(s) in the antibody or antigen-binding fragment are taken from the FR region(s) of a selected human subgroup consensus sequence that has an HVR1 and/or HVR2 sequence that has the most sequence identity to the HVR1 and/or HVR2 of the antibody or antibody binding fragment.

In the least, Chen et al. does not teach selecting positions for substitution that differ from the selected human subgroup consensus sequence or substituting the amino acid found at the corresponding position in selected human consensus subgroup. Chen et al teach substituting FR residues randomly using phage display techniques.

Therefore, Chen et al. do not disclose each and every claimed element, and as such, do not anticipate the claimed subject matter. Applicants respectfully request removal of this rejection.

Summary

Applicants submit that the claims of the present application are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicant's representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Respectfully submitted,

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Date: Oct. 2, 2006

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